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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,058	11/30/2001	David W. Threadgill	421/34/2	6701

EXAMINER
SHAW, AMANDA MARIE

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
02/01/2008	PAPER

25297 7590 02/01/2008
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/998,058	THREADGILL ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-27,46,48-53,60-74,76 and 77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-27, 46, 48-53, 60-74, and 76-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2007 has been entered.

Claims 1, 3-27, 46, 48-53, and 60-74, and 76-77 are currently pending. Claims 1, 8, 10, 11, 15, and 46 have been amended. Therefore Claims 1, 3-27, 46, 48-53, and 60-74, and 76-77 will be addressed herein.

2. It is noted that the interview record is complete.

Withdrawn Rejections

3. The rejections made under 35 USC 102 (a) and (b) in sections 3 and 4 of the Office Action of June 6, 2007 are withdrawn in view of the Applicants arguments.

The rejection made under 35 USC 103 (a) in section 6 of the Office Action of June 6, 2007 is withdrawn in view of the Applicants arguments.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-10, 15, 19, 20-21, 60, 64-67 and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Gora-Maslak (Psychopharmacology 1991).

Regarding Claims 1, 60, and 64 Gora-Maslak teaches methods in which recombinant inbred strains are used to identify quantitative trait loci in psychopharmacology (title). Gora-Maslak teaches that there is clearly a need to increase the power of the RI QTL approach in order the detect QTL that account for small amounts of variance. Gora-Maslak suggests one option is to study F_1 strains derived from crosses among existing RI strains. For example, with 26 RI strains as in the case of BXD, 325 nonreciprocal strains could be generated. For a particular marker half of the F_1 strains derived from crosses between RI strains are expected to be homozygous and the other half are expected to be heterozygous (page 422, col 2). Thus Gora-Maslak teaches a population of genetically diverse individuals since Gora-Maslak teaches that half of the F_1 strains derived from crosses between RI strains are expected to be heterozygous (i.e., genetically diverse). Further this population is considered renewable because the population can be regenerated by crossing the same RI strains over and over again. In the instant case the renewable population of genetically diverse individuals comprises genetically diverse individuals that were produced by crossing different recombinant inbred lines for one generation. Gora-Maslak suggests using these strains for QTL analysis which includes mapping the

genomes of individuals in a population and identifying a genetic locus that modulates the phenotype by mapping (see Tables 1-3 which show genetic loci associated with certain phenoytpes).

Regarding Claims 3-7 and 65 Gora-Maslak teaches a method that uses BXD RI strains to identify QTL in psychopharmacology (abstract). These strains are derived from mice which are considered diploid organisms, animals, mammals, and rodents.

Regarding Claims 8-9 Gora-Maslak teach a method wherein the recombinant inbred lines comprise less than about 500 lines and less than about 100 lines, since Gora-Maslak teaches the use of a BXD series of 26 RI strains (pages 422, col 2).

Regarding Claim 10 Gora-Maslak teaches a method that uses BXD RI strains. These RI strains were developed from the cross between C57BL/6J and DBA/2J (both of which are non recombinant parent lines) (abstract).

Regarding Claim 15 Gora-Maslak teaches a method wherein the panel of cell lines is derived from recombinant inbred line crosses since Gora-Maslak teaches that they studied F_1 strains derived from crosses among existing RI strains (page 422, col 2).

Regarding Claim 19 Gora-Maslak teaches that the essence of QTL association analysis for a quantitative trait is simply to correlated allelic variation with phenotypic variability in a population (page 414, col 2). Thus Gora-Maslak teaches a method wherein mapping comprises analysis of genetic polymorphisms segregating in the renewable population.

Regarding Claims 20-21 and 66-67 Gora-Maslak teaches that they studied six different phenotypes i.e., amphetamine hyperthermia, alcohol acceptance, low does

alcohol sensitivity, alcohol withdrawal, morphine consumption, and quinine consumption. In the instant case they are considered physiological phenotypes. It is noted that claims 21 and 67 further define molecular phenotypes but since claims 20 and 66 never actually require the phenotype to be a molecular phenotype, Gora-Maslak isnt required to teach a molecular pheontype.

Regarding Claims 27 and 73 Gora-Maslak identified two or more genetic loci that modulate each of the six phenotypes studies. (Tables 1-3).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 11-14, 16-18, 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gora-Maslak (Psychopharmacology 1991) in view of Talbot (Nature Genetics 1999).

The teachings of Gora-Maslak are presented above.

Gora-Maslak describes how recombinant inbred lines are generated. Specifically the references states that two parental inbred strains are crossed to produce an F_1 population which is genetically uniform because each individual has one allele from one parent and one from the other parent for any locus at which the two inbred strains differ. Then these animals are crossed to produce an F_2 population which is genetically segregated. Several RI lines are then derived from this F_2 population by mating brothers and sisters and continuing this inbreeding for many generations.

Gora-Maslak does not teach a method wherein the recombinant inbred lines are derived from at least 3 different non recombinant parent lines, at least 4 different non recombinant parent lines or at least 8 different non recombinant parent lines. Further Gora-Maslak does not teach a method wherein at least one of the at least three non recombinant parent lines is selected from mouse lines C57BL/6, BALB/c, C3H, A, 129, and DBA/2.

However Talbot teaches a method in which an eight way cross of C57BL/6, BALB/c, RIII, AKR, DBA/2, I, A/J, and C3H was performed. Thus Talbot teaches a method in which eight different non recombinant parent lines were crossed.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gora-Maslak by using recombinant inbred lines derived from at least 8 different non recombinant parent lines for the expected benefit of creating more diverse progeny. Further the claimed method would have been obvious because the technique of crossing 8 different non recombinant parent lines was part of the ordinary capabilities of a person of ordinary skill in the art. Additionally the technique of making RI lines was part of the ordinary capabilities of a person of ordinary skill in the art. Since all of the claimed elements were known in the prior art, one skilled in the art could have combined these techniques and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

7. Claims 22-26, 46, 48, 50-53, 68-72, 74, and 76-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gora-Maslak (Psychopharmacology 1991) in view of Diehl (PNAS 1997).

The teachings of Gora-Maslak are presented above.

Regarding Claims 22-26 and 68-72 Gora-Maslak does not teach a method wherein the phenotype being studied is modulated by a non genetic factor. Gora-Maslak does not teach a method wherein the phenotype being studied is modulated by

an interaction between two or more non genetic factors. Gora-Maslak does not teach a method wherein the non genetic factor is an environmental condition or drug exposure. Gora-Maslak does not teach a method wherein the phenotype being studied is modulated by an interaction between a genetic locus and a non genetic factor. Gora-Maslak does not teach a method wherein the non genetic factor is an environmental condition or drug exposure.

However Diehl teaches a method for identifying multiple genetic loci that modulate the phenotype of facial clef ting. Diehl studied two different phenotypes, cleft lip and cleft palate (abstract). Diehl teaches the cleft lip phenotype is modulated by several non-genetic factors (i.e., exposure to ethanol, trimethadione, and phenytoin) and that the cleft palate phenotype is also modulated by several non genetic factors (i.e. exposure to aminopterin, retinoic acid, and 6-aminonicotinamide) (page 5231, col 2). Thus Diehl teaches a method wherein the phenotype being studied is modulated by an interaction between two or more non genetic factors, wherein the non genetic factors are exposure to different drugs. Diehl further states that both cleft lip and cleft palate have a highly complex etiology, with both multiple genetic loci and exposure to teratogens influencing susceptibility (abstract). Thus Diehl teaches a method wherein the phenotype being studied is modulated by an interaction between a genetic locus and a non genetic factor.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to have applied the QTL mapping method of Gora-Maslak, which uses F_1 strains derived from crosses among existing RI strains, to study

the etiology of cleft lip and cleft palate. Gora-Maslak teaches that although 25 RI F_1 strains do not provide information equivalent to 25 RI strains, the possibility of much larger sample sizes for RI F1 strains more than compensates for the modest genotypic correlation among the F1 strains. In this ways the use of large numbers of RI F1 strains can greatly increase the power to detect QTL responsible for small amount of variance (page 423, col 1). Thus one would have been motivated to combine the methods of Gora-Maslak and Diehl for the benefit of increasing the power of the RI QTL approach in order to detect QTL that account for small amounts of variance.

Regarding Claims 46, 48, 50-53, 74 and 76-77 Gora-Maslak teaches methods in which recombinant inbred strains are used to identify quantitative trait loci in psychopharmacology (title). Gora-Maslak teaches that there is clearly a need to increase the power of the RI QTL approach in order the detect QTL that account for small amounts of variance. Gora-Maslak suggests one option is to study F_1 strains derived from crosses among existing RI strains. For example, with 26 RI strains as in the case of BXD, 325 nonreciprocal strains could be generated. For a particular marker half of the F_1 strains derived from crosses between RI strains are expected to be homozygous and the other half are expected to be heterozygous (page 422, col 2). Thus Gora-Maslak teaches a population of genetically diverse individuals since Gora-Maslak teaches that half of the F_1 strains derived from crosses between RI strains are expected to be heterozygous (i.e., genetically diverse). Further this population is considered renewable because the population can be regenerated by crossing the same RI strains over and over again. In the instant case the renewable population of

genetically diverse individuals comprises genetically diverse individuals that were produced by crossing different recombinant inbred lines for one generation. Gora-Maslak suggests using these strains for QTL analysis which is considered a mapping method because this method is used to identifying regions of DNA that are associated with a particular phenotypic trait.

Gora-Maslak does not teach a method wherein the renewable population is provided with a non genetic factor and identifying an interaction between a genetic locus and the non genetic factor that modulates the phenotype. Gora-Maslak does not teach a method wherein the phenotype is a visible phenotype. Gora-Maslak does not teach a method further comprising identifying an interaction among two or more genetic loci and a non genetic factor. Gora-Maslak does not teach a method further comprising identifying an interaction among a genetic locus and two more non genetic factors. Gora-Maslak does not teach a method wherein the non genetic factor is an environmental condition or drug exposure. Gora-Maslak does not teach a method further comprising identifying an interaction among two or more genetic loci and two or more non genetic factors. Further Gora-Maslak does not teach a method comprising identifying the genetic locus with which the non-genetic factor interacts to modulate the phenotype.

However Diehl teaches a method for identifying multiple genetic loci that modulate the phenotype of facial clefting. Diehl studied two different visible phenotypes, cleft lip and cleft palate (abstract). Diehl teaches the cleft lip phenotype is modulated by several non-genetic factors (i.e., exposure to ethanol, trimethadione, and

phenytoin) and that the cleft palate phenotype is also modulated by several non genetic factors (i.e. exposure to aminopterin, retinoic acid, and 6-aminonicotinamide) (page 5231, col 2). Thus Diehl teaches a method wherein the phenotype being studied is modulated by an interaction between two or more non genetic factors, wherein the non genetic factors are exposure to different drugs. Diehl further states that both cleft lip and cleft palate have a highly complex etiology, with both multiple genetic loci and exposure to teratogens influencing susceptibility (abstract). Thus Diehl teaches a method wherein the phenotype being studied is modulated by an interaction between a genetic locus and a non genetic factor. Specifically Diehl describes an experiment in which RI strains were either treated with phenytoin (which induces cleft lip) or 6-AN which induces cleft palate). (page 5232, col 1). These strains were then examined for 361 markers (page 5232, col 2). The results are presented in Table 2 and suggest that multiple loci are involved. Thus Diehl teaches a method in which a population is provided with a non genetic factor and an interaction between a genetic locus and the non genetic factor that modulates the phenotype is identified.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to have applied the QTL mapping method of Gora-Maslak, which uses F_1 strains derived from crosses among existing RI strains, to study the etiology of cleft lip and cleft palate. Gora-Maslak teaches that although 25 RI F_1 strains do not provide information equivalent to 25 RI strains, the possibility of much larger sample sizes for RI F1 strains more than compensates for the modest genotypic correlation among the F1 strains. In this ways the use of large numbers of RI F1 strains

can greatly increase the power to detect QTL responsible for small amount of variance (page 423, col 1). Thus one would have been motivated to combine the methods of Gora-Maslak and Diehl for the benefit of increasing the power of the RI QTL approach in order to detect QTL that account for small amounts of variance.

8. Claims 21 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gora-Maslak (Psychopharmacology 1991) in view of Dumas (Journal of Hypertension 2000).

The teachings of Gora-Maslak are presented above.

Regarding Claims 21 and 67, Gora-Maslak does not teach for identifying a genetic locus that modulates a molecular phenotype by mapping.

However Dumas teaches a method for identifying the genetic locus which is associated with hsp expression by mapping. The method used recombinant inbred rat strains (abstract). In the instant case the hsp expression is being interpreted as a molecular phenotype.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to have applied the QTL mapping method of Gora-Maslak, which uses F_1 strains derived from crosses among existing RI strains, to study the genetic locus associated with hsp expression. Gora-Maslak teaches that although 25 RI F_1 strains do not provide information equivalent to 25 RI strains, the possibility of much larger sample sizes for RI F1 strains more than compensates for the modest genotypic correlation among the F1 strains. In this ways the use of large numbers of RI

F1 strains can greatly increase the power to detect QTL responsible for small amount of variance (page 423, col 1). Thus one would have been motivated to combine the methods of Gora-Maslak and Dumas for the benefit of increasing the power of the RI QTL approach in order to detect QTL that account for small amounts of variance.

9. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gora-Maslak (Psychopharmacology 1991) in view of Diehl (PNAS 1997) as applied to claims 46 and 48 above, and in further view of Dumas (Journal of Hypertension 2000).

The teachings of Gora-Maslak and Diehl are presented above.

Regarding Claim 49 the combined references do not teach for identifying a genetic locus that modulates a molecular phenotype by mapping.

However Dumas teaches a method for identifying the genetic locus which is associated with hsp expression by mapping. The method used recombinant inbred rat strains (abstract). In the instant case the hsp expression is being interpreted as a molecular phenotype.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to have applied the QTL mapping method of Gora-Maslak, which uses F_1 strains derived from crosses among existing RI strains, to study the genetic locus associated with hsp expression. Gora-Maslak teaches that although 25 RI F_1 strains do not provide information equivalent to 25 RI strains, the possibility of much larger sample sizes for RI F1 strains more than compensates for the modest

genotypic correlation among the F1 strains. In this ways the use of large numbers of RI F1 strains can greatly increase the power to detect QTL responsible for small amount of variance (page 423, col 1). Thus one would have been motivated to combine the methods of Gora-Maslak and Dumas for the benefit of increasing the power of the RI QTL approach in order to detect QTL that account for small amounts of variance.

Conclusion

10. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER